REMARKS

Upon entry of the foregoing amendments, allowed claims 33, 34 and 49-52, currently rejected claims 54, 55, 57 and 58, and new claims 60 and 61 are pending.

Independent claims 53 and 56 are cancelled without prejudice or disclaimer.

Claims 54 and 57 are amended to depend from, respectively, new independent claims 60 and 61 instead.

New independent claims 60 and 61 are added to more particularly point out and distinctly claim the subject matter that Applicants regard as their invention. Support for claim 60 is found at least in the specification at page 14, line 20, to page 15, line 8. Support for claim 61 is found at least in the specification at page 11, line 11, to page 12, line 4. The proper written description support for claims 60 and 61 is discussed more fully below.

Applicants submit that the claim amendments do not include new matter and are supported by the originally filed specification. Entry of the claim amendments is respectfully requested.

The Examiner is reminded that there are no outstanding prior art rejections.

The Office Action contains rejections to claims 53-58 under 35 USC 112, first paragraph, based on lack of enablement and written description support and new matters for independent claims 53 and 56. These rejections are moot in view of the cancellation of claims 53 and 56 after entry of the claim amendments.

New independent claims 60 and 61, and their dependent claims 54, 55, 57 and 58 are allowable for at least the following reasons.

Correlation between structure and function

The Examiner asserts that the specification has not made a correlation between structure and function, and has not shown which amino acids within the amino acid sequence can be changed such that the protein still retains its biological function of eliciting an immune response. Applicants respectfully disagree.

As described throughout the specification, Applicants point out that they have discovered that NhhA, a surface antigen, has regions that are variable, i.e., V1-V4, and regions that are conserved, i.e., C1-C5, among different strains of *N. meningitidis*. The variable regions may contribute to strain-specific immune responses. In an effort to obtain a vaccine that is capable of eliciting an immune response to multiple strains of *N. meningitidis,* Applicants designed and

produced modified NhhA polypeptides that contain one or more conserved regions, and a deletion or substitution of one or more non-conserved amino acids in the variable regions, to elicit an immune response primarily against conserved epitopes in the conserved regions.

As illustrated in Example 4, Applicants designed and produced a modified NhhA polypeptide comprising SEQ ID NO:23. The modified protein includes amino acids 1-54 and 134-592 of the wild-type PMC21 NhhA polypeptide sequence, thus a deletion of the majority of the V1 region, all of the V2 and C2 regions, and part of the C3 region of the wild-type PMC21. SEQ ID NO:35 is the mature form of SEQ ID NO:23 that does not contain the signal sequence.

As shown in Example 10, the modified protein elicited an immune response in mice, resulted in production of antibodies recognizing the full length PMC21 NhhA polypeptide (Fig. 13). Results of Example 10 showed that it is feasible to elicit an immune response in an animal against the full length PMC21 Nhh polypeptide, and thus the *N. meningitidis* containing the full length NhhA polypeptide, by immunizing the animal with a modified NhhA polypeptide, such as that of SEQ ID NO:23 or 35, that contains mainly the conserved regions of the NhhA polypeptide.

It is noted that the variable regions (V3, V4 and a few amino acids in V1) in SEQ ID NO:23 or 35 constitute only about 40 amino acids out of the approximately 500 amino acids of the sequence. The rest of the protein variant, i.e., about 460 amino acids of the total 500 amino acids of the sequence, remains the same as that in SEQ ID NO:23 or 35, and the full length NhhA protein. Thus, proteins of claims 60 and 61 may share common immunogenic epitopes with those of SEQ ID NO:23 or 35, and the full length NhhA protein, in this common sequence of 460 amino acids. Accordingly, proteins of claims 60 and 61, like SEQ ID NO:23 or 35 shown in Example 10, may elicit an immune response to the full length NhhA protein, and thus the *N. meningitidis* containing the full length NhhA polypeptide.

Proteins of claims 60 and 61, having 500 amino acids, may contain multiple immunogenic epitopes. Even assuming a conservative substitution or a deletion of one or more amino acids within the variable regions of SEQ ID NO:23 or 35 affects immune responses to epitopes in the variable regions, such change would very unlikely abolish immune responses to epitopes in the sequence containing the unchanged 460 amino acids. Thus, such change is highly unlikely to completely render proteins of claims 60 and 61 non-immunogenic to the full length NhhA protein or the *N. meningitidis* containing the full length NhhA polypeptide.

Indeed, by having deletions or modifications of non-conserved amino acids in the variable regions, the modified surface antigen NhhA protein may elicit less strain specific immune responses to epitopes within the variable regions than what would be expected from a corresponding wild-type NhhA. However, because the conserved regions are unchanged, the modified surface protein may be useful in vaccines for effective immunization against a broader spectrum of *N. meningitidis* strains that contain the conserved regions. Accordingly, the specification does provide guidance with respect to the portions of SEQ ID NOS:23 or 35 that are to be conserved (*i.e* "*conserved regions*") and those which may be varied (*i.e* "*variable regions*") for the purpose of the claimed invention. Consistent with this, claims 60 and 61 recite that only V region amino acids may be conservatively substituted and deleted, respectively.

Claims 60 and 61 are fully supported by the specification

Claim 60 is directed to a protein variant that comprises at least one conservative amino acid substitution in a variable region of SEQ ID NO:23 or SEQ ID NO:35. Claim 61 is directed to an isolated protein that comprises at least one deletion of an amino acid in a variable region of SEQ ID NO:23 or SEQ ID NO:35. These claims are fully supported by the specification, because a person skilled in the art, reading the specification, could readily discern that Applicants were in possession of the invention at the time of the application.

To show that Applicant was in possession of the invention, *ipsis verbis* recitation of the claimed protein is not required. The specification describes SEQ ID NO:23 or 35 as examples of the modified NhhA polypeptide. The specification also describes that SEQ ID NO:23 and 25 contain variable regions with known sequences.

The specification describes variants of the modified NhhA polypeptide and how to make them. The specification, particularly at page 14, lines 22-25, Example 4, FIG. 1 and Table 2, provides an explicit description of variable regions of SEQ ID NOS:23 and 35 and conservative amino acid substitutions that may be made in the V region amino acids (Table 2). Therefore, it is readily apparent to those skilled in the art that at the time of the invention, Applicants were in possession of a protein variant of SEQ ID NO:23 or SEQ ID NO:35 comprising at least one conservative amino acid substitution in a variable region of SEQ ID NO:23 or SEQ ID NO:35.

The specification further indicates the desirability to make deletions in the variable regions in order to elicit immune response primarily against conserved epitopes in the conserved regions. The specification also provides a more than adequate description of how deletions in

the variable regions can be made, e.g., in working Examples. Therefore, it is readily apparent to those skilled in the art that at the time of the invention, Applicants were in possession of a protein comprising at least one deletion of an amino acid in a variable region of SEQ ID NO:23 or SEQ ID NO:35.

Applicants respectfully submit that the written description requirement does not require the Applicants to provide "*longhand*" recitation of multiple examples of variant sequences when these are directly and unambiguously derivable from the sequence information provided by the written description as a whole. In other words, "*longhand*" recitation of multiple examples of variant sequences would merely constitute a reorganization of information already provided by the written description when considered as a whole.

Claims 60 and 61 are fully enabled by the specification

By definition, a conservative substitution would result in broadly similar properties in the activity of a polypeptide comprising the conservative substitution. A protein variant in claim 60 contains one or more conservative substitutions only in the about 40 amino acids in the variable regions of SEQ ID NO: 23 or 35. By referring to Table 2 and the amino acid sequences set forth in SEQ ID NOS:23-35, a person of ordinary skill in the art could replace any of the V regions of SEQ ID NOS:23-35 with an appropriate conservative substitution described in Table 2. In view of the discussion under Correlation between structure and function above, conservative substitutions of one or more amino acids of the about 40 amino acids are highly unlikely to significantly adversely affect the immune responses to epitopes in the about 460 amino acids of the rest of the protein variant.

A deletion of one or more amino acids of the about 40 amino acids in the variable region is also highly unlikely to significantly adversely affect the immune responses to the about 460 amino acids of the rest of the protein. Indeed, as shown in Example 10, the deletion of about 80 amino acids from the full length NhhA that contains V1 and V2, did not significantly adversely affect the immune responses to the rest of the sequence in SEQ ID NO:23 or 35, which comprises mainly the C4 and C5 regions. Such a deletion mutant elicited an immune response in an animal against the full length PMC21 NhhA polypeptide, and thus the *N. meningitidis* containing the full length Nhh polypeptide.

By referring to the sequence lineup in FIG. 1, a person of ordinary skill in the art could decide which V region amino acids tend to be more or less conserved/variable between *N.*

meningitidis strains, thereby providing further guidance as to which amino acid should deleted or be substituted with what in order to better preserve the overall structure of the protein and have less effect on the immune response to the conserved regions.

Conservative substitution or deletion of one or more amino acids can be achieved by methods known in the art, such as site directed mutagenesis, or other methods taught in the specification, such as the Examples.

Further, there are predictive methods of defining the immunogenicity of a protein without having to resort to the kind of empirical, undue experimentation referred to by the Examiner. These were set forth in Applicant's response to the previous Office Action and apply equally here. Also, by following procedures described in the present invention, such as that in Example 10, the immunogenicity of a protein variant can be tested in an animal to confirm that the protein variant elicits an immune response against the full length mature NhhA, and thus the *N. meningitidis*. Such tests are routine to a person skilled in the art, not undue.

35 USC 112, first paragraph, does not prohibit some experimentation being required on the part of the skilled person, only that undue experimentation should not be required.

Accordingly, Applicants respectfully submit that claims 60 and 61 are fully enabled and described in the specification as originally filed.

Dependent claims 54, 55, 57 and 58

Claims 54 and 57 recite a pharmaceutical composition comprising the isolated protein variant of claims 60 and 61, respectively, and a pharmaceutically-acceptable carrier, diluent, or excipient. The specification describes and teaches pharmaceutical compositions comprising a modified NhhA protein. Because the proteins of claim 60 and 61 are fully enabled and described as discussed above, claims 54 and 57 are also fully enabled and described.

Claims 55 and 58 recite that the pharmaceutical composition of claim 54 and 57, respectively, is immunogenic. As discussed above, a protein variant of claim 60 or the protein of claim 61 is immunogenic at least by the presence of the about 460 not substituted amino acids in the protein variant, and claims 54 and 57 are fully enabled and described. Thus, claims 55 and 58 are also fully enabled and described.

Reconsideration and withdrawal of all of the rejections are respectfully solicited.

Applicants respectfully submit that the present application is now in condition for allowance. Reconsideration and withdrawal of all of the objections and rejections, and an early Notice of Allowance of all pending claims are respectfully solicited.

Applicants respectfully request that the Examiner grant to their undersigned attorney an interview, during which a discussion may help overcome any misunderstandings about the application and claims and any suggestions may be presented for advancing the prosecution of this application containing claims of the scope sought but not yet allowed, as well as the allowed claims. The Examiner is requested to contact the undersigned attorney to arrange an interview at a mutually convenient date and time in the relatively near future.

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